Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease—mineral and bone disorder (CKD-MBD).

Bibliographic Source(s)

Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney diseaseâ€"mineral and bone disorder (CKD-MBD). Kidney Int Suppl. 2017 Jul;7(1):1-59. [173 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int. 2009 Aug;76(Suppl 113):S1-130. [477 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

NEATS Assessment

National Guideline Clearinghouse (NGC) has assessed this guideline's adherence to standards of trustworthiness, derived from the Institute of Medicine's report Clinical Practice Guidelines We Can Trust.

= Poor = Fair = Good = Very Good = Excellent

Assessment	Standard of Trustworthiness
NO	Disclosure of Guideline Funding Source
	Disclosure and Management of Financial Conflict of Interests

	Guideline Development Group Composition
YES	Multidisciplinary Group
YES	Methodologist Involvement
▮▮▯▯▯	Patient and Public Perspectives
	Use of a Systematic Review of Evidence
▮▮▮▮▮	Search Strategy
▮▮▮▮▮	Study Selection
▮▮▮▮▮	Synthesis of Evidence
	Evidence Foundations for and Rating Strength of Recommendations
▮▮▮▮▮	Grading the Quality or Strength of Evidence
▮▮▮▮▮	Benefits and Harms of Recommendations
▮▮▮▮▮	Evidence Summary Supporting Recommendations
▮▮▮▮▮	Rating the Strength of Recommendations
▮▮▮▮▮	Specific and Unambiguous Articulation of Recommendations
▮▮▮▮▯	External Review
▮▯▯▯▯	Updating

Recommendations

Major Recommendations

Definitions of the strength of recommendation (Level 1, Level 2, or Not Graded), and the quality of the supporting evidence (A-D) are provided at the end of the "Major Recommendations" field. Refer to the original guideline document for nomenclature used by Kidney Disease: Improving Global Outcomes.

Diagnosis of Chronic Kidney Disease–Mineral and Bone Disorder (CKD–MBD): Biochemical Abnormalities

The Work Group recommends monitoring serum levels of calcium, phosphorus, parathyroid hormone (PTH), and alkaline phosphatase activity beginning in chronic kidney disease (CKD) G3a (1C). In children, the Work Group suggests such monitoring beginning in CKD G2 (2D).

In patients with CKD G3a–G5D, it is reasonable to base the frequency of monitoring serum calcium, phosphorus, and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD (Not Graded). Reasonable monitoring intervals would be:

In CKD G3a–G3b: for serum calcium and phosphate, every 6 to 12 months; and for PTH, based on baseline level and CKD progression.

In CKD G 4: for serum calcium and phosphate, every 3 to 6 months; and for PTH, every 6 to 12 months.

In CKD G5, including 5D: for serum calcium and phosphate, every 1 to 3 months; and for PTH, every 3 to 6 months.

In CKD G4–G5D: for alkaline phosphatase activity, every 12 months, or more frequently in the presence of elevated PTH (see "Diagnosis of CKD–MBD: Bone," below).

In CKD patients receiving treatments for CKD–MBD, or in whom biochemical abnormalities are identified, it is reasonable to increase the frequency of measurements to monitor for trends and treatment efficacy and side effects (Not Graded).

In patients with CKD G3a–G5D, the Work Group suggests that 25-hydroxyvitamin D [25(OH)D] (calcidiol) levels might be measured, and repeated testing determined by baseline values and therapeutic interventions (2C). The Work Group suggests that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (2C).

In patients with CKD G3a–G5D, the Work Group recommends that therapeutic decisions be based on trends rather than on a single laboratory value, taking into account all available CKD–MBD assessments (1C).

In patients with CKD G3a–G5D, the Work Group suggests that individual values of serum calcium and phosphorus, evaluated together, be used to guide clinical practice rather than the mathematical construct of calcium–phosphorus product (Ca x P) (2D).

In reports of laboratory tests for patients with CKD G3a–G5D, the Work Group recommends that clinical laboratories inform clinicians of the actual assay method in use and report any change in methods, sample source (plasma or serum), or handling specifications to facilitate the appropriate interpretation of biochemistry data (1B).

Diagnosis of CKD–MBD: Bone

In patients with CKD G3a–G5D with evidence of CKD–MBD and/or risk factors for osteoporosis, the Work Group suggests bone mineral density (BMD) testing to assess fracture risk if results will impact treatment decisions (2B).

In patients with CKD G3a–G5D, it is reasonable to perform a bone biopsy if knowledge of the type of renal osteodystrophy will impact treatment decisions (Not Graded).

In patients with CKD G3a–G5D, the Work Group suggests that measurements of serum PTH or bone-specific alkaline phosphatase can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover (2B).

In patients with CKD G3a–G5D, the Work Group suggests not to routinely measure bone-derived turnover markers of collagen synthesis (such as procollagen type I C-terminal propeptide) and breakdown (such as type I collagen cross-linked telopeptide, cross-laps, pyridinoline, or deoxypyridinoline) (2C).

The Work Group recommends that infants with CKD G2–G5D should have their length measured at least quarterly, while children with CKD G2–G5D should be assessed for linear growth at least annually (1B).

Diagnosis of CKD–MBD: Vascular Calcification

In patients with CKD G3a–G5D, the Work Group suggests that a lateral abdominal radiograph can be used to detect the presence or absence of vascular calcification, and an echocardiogram can be used to detect the presence or absence of valvular calcification, as reasonable alternatives to computed tomography-based imaging (2C).

The Work Group suggests that patients with CKD G3a–G5D with known vascular or valvular calcification be considered at highest cardiovascular risk (2A). It is reasonable to use this information to guide the management of CKD–MBD (Not Graded).

Treatment of CKD–MBD Targeted at Lowering High Serum Phosphate and Maintaining Serum Calcium

In patients with CKD G3a–G5D, treatments of CKD–MBD should be based on serial assessments of phosphate, calcium, and PTH levels, considered together (Not Graded).

In patients with CKD G3a–G5D, the Work Group suggests lowering elevated phosphate levels toward the normal range (2C).

In adult patients with CKD G3a–G5D, the Work Group suggests avoiding hypercalcemia (2C). In children with CKD G3a–G5D, the Work Group suggests maintaining serum calcium in the age-appropriate normal range (2C).

In patients with CKD G5D, the Work Group suggests using a dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) (2C).

In patients with CKD G3a–G5D, decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphate (Not Graded).

In adult patients with CKD G3a–G5D receiving phosphate-lowering treatment, the Work Group suggests restricting the dose of calcium-based phosphate binders (2B). In children with CKD G3a–G5D, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels (Not Graded).

In patients with CKD G3a–G5D, the Work Group recommends avoiding the long-term use of aluminum-containing phosphate binders and, in patients with CKD G5D, avoiding dialysate aluminum contamination to prevent aluminum intoxication (1C).

In patients with CKD G3a–G5D, the Work Group suggests limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments (2D). It is reasonable to consider phosphate source (e.g., animal, vegetable, additives) in making dietary recommendations (Not Graded).

In patients with CKD G5D, the Work Group suggests increasing dialytic phosphate removal in the treatment of persistent hyperphosphatemia (2C).

Treatment of Abnormal PTH Levels in CKD–MBD

In patients with CKD G3a–G5 not on dialysis, the optimal PTH level is not known. However, the Work Group suggests that patients with levels of intact PTH (iPTH) progressively rising or persistently above the upper normal limit for the assay be evaluated for modifiable factors, including hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency (2C).

In adult patients with CKD G3a–G5 not on dialysis, the Work group suggests that calcitriol and vitamin D analogs not be routinely used (2C). It is reasonable to reserve the use of calcitriol and vitamin D analogs for patients with CKD G4–G5 with severe and progressive hyperparathyroidism (Not Graded). In children, calcitriol and vitamin D analogs may be considered to maintain serum calcium levels in the age-appropriate normal range (Not Graded).

In patients with CKD G5D, the Work Group suggests maintaining iPTH levels in the range of approximately 2 to 9 times the upper normal limit for the assay (2C).

The Work Group suggests that marked changes in PTH levels in either direction within this range prompt an initiation or change in therapy to avoid progression to levels outside of this range (2C).

In patients with CKD G5D requiring PTH-lowering therapy, the Work Group suggests calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics with calcitriol or vitamin D analogs (2B).

In patients with CKD G3a–G5D with severe hyperparathyroidism (HPT) who fail to respond to medical or pharmacological therapy, the Work Group suggests parathyroidectomy (2B).

Treatment of Bone with Bisphosphonates, Other Osteoporosis Medications, and Growth Hormone

In patients with CKD G1–G2 with osteoporosis and/or high risk of fracture, as identified by World Health Organization (WHO) criteria, the Work Group recommends management as for the general population (1A).

In patients with CKD G3a–G3b with PTH in the normal range and osteoporosis and/or high risk of fracture, as identified by WHO criteria, the Work Group suggests treatment as for the general population (2B).

In patients with CKD G3a–G5D with biochemical abnormalities of CKD–MBD and low BMD and/or fragility fractures, the Work Group suggests that treatment choices take into account the magnitude and reversibility of the biochemical abnormalities and the progression of CKD, with consideration of a bone biopsy (2D).

In children and adolescents with CKD G2–G5D and related height deficits, the Work Group

recommends treatment with recombinant human growth hormone when additional growth is desired, after first addressing malnutrition and biochemical abnormalities of CKD–MBD (1A).

Evaluation and Treatment of Kidney Transplant Bone Disease

In patients in the immediate post–kidney-transplant period, the Work Group recommends measuring serum calcium and phosphate at least weekly, until stable (1B).

In patients after the immediate post–kidney-transplant period, it is reasonable to base the frequency of monitoring serum calcium, phosphate, and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD (Not Graded). Reasonable monitoring intervals would be:

- In CKD G1T–G3bT, for serum calcium and phosphate, every 6 to 12 months; and for PTH, once, with subsequent intervals depending on baseline level and CKD progression.
- In CKD G4T, for serum calcium and phosphate, every 3 to 6 months; and for PTH, every 6 to 12 months.
- In CKD G5T, for serum calcium and phosphate, every 1 to 3 months; and for PTH, every 3 to 6 months.
- In CKD G3aT–G5T, measurement of alkaline phosphatases annually, or more frequently in the presence of elevated PTH (see "Diagnosis of CKD–MBD: Bone," above).

In CKD patients receiving treatments for CKD–MBD, or in whom biochemical abnormalities are identified, it is reasonable to increase the frequency of measurements to monitor for efficacy and side effects (Not Graded). It is reasonable to manage these abnormalities as for patients with CKD G3a–G5 (Not Graded) (see "Treatment of CKD–MBD Targeted at Lowering High Serum Phosphate and Maintaining Serum Calcium" and "Treatment of Abnormal PTH Levels in CKD–MBD," above).

In patients with CKD G1T–G5T, the Work Group suggests that 25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and interventions (2C).

In patients with CKD G1T–G5T, the Work Group suggests that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (2C).

In patients with CKD G1T–G5T with risk factors for osteoporosis, the Work Group suggests that BMD testing be used to assess fracture risk if results will alter therapy (2C).

In patients in the first 12 months after kidney transplant with an estimated glomerular filtration rate greater than approximately 30 ml/min per 1.73 m^2 and low BMD, the Work Group suggests that treatment with vitamin D, calcitriol/alfacalcidol, and/or antiresorptive agents be considered (2D).

- The Work Group suggests that treatment choices be influenced by the presence of CKD–MBD, as indicated by abnormal levels of calcium, phosphate, PTH, alkaline phosphatases, and 25(OH)D (2C).
- It is reasonable to consider a bone biopsy to guide treatment (Not Graded).

There are insufficient data to guide treatment after the first 12 months.

In patients with CKD G4–G5T with known low BMD, the Work Group suggests management as for patients with CKD G4–G5 not on dialysis, as detailed in "Treatment of CKD–MBD Targeted at Lowering High Serum Phosphorus and Maintaining Serum Calcium" and "Treatment of Abnormal PTH Levels in CKD–MBD," above (2C).

Definitions

Strength of Recommendation

	Implications		
Grade*	**Patients**	**Clinicians**	**Policy**
Level 1 "The Work Group recommends"	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.

Grade*	Implications		
	Patients	Clinicians	Policy
Level 2 "The Work Group suggests"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

*The additional category "not graded" is used, typically, to provide guidance based on common sense or when the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

Final Grade for Overall Quality of Evidence

Grade	Quality of Evidence	Meaning
A	High	The Work Group is confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very Low	The estimate of effect is very uncertain, and often will be far from the truth.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

- Chronic kidney disease–mineral and bone disorder (CKD–MBD)
- Complications of CKD-BMD including hyperparathyroidism, osteoporosis and osteoporotic fractures, and vascular or valvular calcification
- Kidney transplant bone disease

Guideline Category

Diagnosis

Evaluation

Management

Prevention

Treatment

Clinical Specialty

Endocrinology

Family Practice

Internal Medicine

Nephrology

Pediatrics

Preventive Medicine

Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

- To update the 2009 clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease—mineral and bone disorder (CKD-MBD)
- To assist practitioners caring for adults and children with CKD, those on chronic dialysis therapy, or individuals with a kidney transplant

Target Population

- Adults and children with chronic kidney disease
- Individuals with a kidney transplant

Interventions and Practices Considered

Diagnosis/Evaluation

Monitoring serum levels of calcium, phosphorus, parathyroid hormone (PTH), 25-hydroxyvitamin D [25(OH)D] (calcidiol), and alkaline phosphatase activity
Monitoring intervals based on stage of chronic kidney disease (CKD) and presence of biochemical abnormalities
Including assay method used in reporting of laboratory test results
Bone mineral density testing
Bone biopsy
Measurement of bone-derived turnover markers of collagen synthesis (not recommended routinely)
Measuring length of infants with CKD G2–G5D
Assessment of linear growth in children with CKD G2–G5D
Lateral abdominal radiograph
Echocardiogram

Treatment/Management

Maintaining normal serum ranges of calcium, phosphorus, and PTH
Phosphate-lowering treatment
Restricting the dose of calcium-based phosphate binders
Avoiding the long-term use of aluminum-containing phosphate binders and dialysate aluminum

contamination
Limiting dietary phosphate intake and increasing dialytic phosphate removal in the treatment of hyperphosphatemia
Evaluation of modifiable factors, including hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency, patients with levels of intact PTH progressively rising or persistently above the upper normal limit for the assay
Calcitriol or vitamin D analogs or calcimimetics (or combinations) in patients with elevated serum PTH
Parathyroidectomy
Treatment of osteoporosis with bisphosphonates or other osteoporosis medications
Considerations for bone biopsy prior to antiresorptive and other osteoporosis therapies
Recombinant human growth hormone for children and adolescents with height deficits
Considerations for evaluation and treatment of bone disease post-kidney transplant

Major Outcomes Considered

- Bone turnover mineralization volume (TMV)
- Bone mineral density/bone mineral content
- Fracture
- Mortality
- Glomerular filtration rate decline
- Cardiovascular and cerebrovascular events
- Vascular and valvular calcification
- Hypercalcemia

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Search Strategy

The Evidence Review Team (ERT) searched MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL) for the date range of December 2006 through September 2015. The December 2006 date provided the recommended 1-year overlap with the end of the previous search. The search yield was also supplemented by articles provided by the Work Group members through February 2017.

The search strategy included Medical Subject Headings (MeSH) and text terms for chronic kidney disease (CKD) and the interventions and markers of interest (see Supplementary Appendix A [see the "Availability of Companion Documents" field]) and was limited to the English language. The ERT also reviewed the list of references that were suggested during the Controversies Conference.

All studies that had been included in the prior guideline were rereviewed to ensure that they met the eligibility criteria.

Inclusion and Exclusion Criteria

With input from the Work Group, the ERT defined the eligibility criteria *a priori*. The eligibility criteria for all studies were: (i) original data published in English, (ii) followed up at least 10 patients with CKD for at least 6 months, and (iii) addressed 1 of the research questions. The minimum mean duration of follow-

up of 6 months was chosen on the basis of clinical reasoning, accounting for the hypothetical mechanisms of action. For treatments of interest, the proposed effects on patient-centered outcomes require long-term exposure and typically would not be evident before several months of follow-up. The question-specific eligibility criteria are provided in Table 3 of the original guideline document, and the overall search yield for the guideline systematic review is summarized in Supplementary Appendix B (see the "Availability of Companion Documents" field).

Two reviewers independently screened titles and abstracts and full-text articles for inclusion. Differences regarding inclusion were resolved through consensus adjudication.

Any study not meeting the inclusion criteria could be cited in the narrative but was not considered part of the body of evidence for a particular recommendation.

Number of Source Documents

117 studies published in 128 articles were included. See Appendix B (see the "Availability of Companion Documents" field) for the summary of search and review process.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) System for Grading Quality of Evidence for an Outcome

Step 1: Starting Grade for Quality of Evidence Based on Study Design	
High for randomized trials	
Moderate for quasi-randomized trials	
Low for observational study	
Very low for any other evidence	
Step 2: Reduce Grade	
Study quality	-1 level if serious limitations -2 levels if very serious limitations
Consistency	-1 level if important inconsistency
Directness	-1 level if some uncertainty -2 levels if major uncertainty
Other	-1 level if sparse or imprecise data -1 level if high probability of reporting bias
Step 3: Raise Grade	
Strength of association	+1 level if strong,[a] no plausible confounders, consistent and direct evidence +2 levels if very strong,[b] no major threats to validity and direct evidence
Other	+1 level if evidence of a dose–response gradient +1 level if all residual plausible confounders would have reduced the observed effect
Final Grade for Quality of Evidence for an Outcome	
High	
Moderate	
Low	
Very low	

[a]Strong evidence of association is defined as 'significant relative risk (RR) of >2 (<0.5)' based on consistent evidence from two or more observational studies, with no plausible confounders.

[b]Very strong evidence of association is defined as 'significant RR of >5 (<0.2)' based on direct evidence with no major threats to validity.

Modified with permission from Uhlig et al. Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006;70: 2058-2065.

Final Grade for Overall Quality of Evidence

Grade	Quality of Evidence	Meaning
A	High	The Work Group is confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very Low	The estimate of effect is very uncertain, and often will be far from the truth.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction

The Evidence Review Team (ERT) modified the online supplementary tables from the prior guideline. One reviewer abstracted data directly into the modified tables, and a second reviewer confirmed the data abstraction. The ERT abstracted data on general study characteristics, participant characteristics, interventions and co-interventions, and outcome measures, including measures of variability.

Two reviewers independently assessed individual study quality using the Cochrane Collaboration's tool for assessing risk of bias for randomized controlled trials (RCTs) and using the Quality in Prognosis Studies tool for observational studies.

The Work Group critically reviewed draft tables, and tables were revised as appropriate.

Evidence Matrices and Evidence Profiles

The ERT created evidence matrices for each of the key outcomes for each research question. For each key outcome, the matrix lists the individual studies, their sample size, follow-up duration, and the individual study quality. The ERT also drafted evidence profiles to display the total number and overall quality of the studies addressing each key outcome for each research question.

Revising Recommendations

In June 2015, the Work Group and the ERT convened a 3-day meeting in Baltimore, MD, to review the summary tables, evidence profiles, and evidence matrices; to decide whether and how the recommendations should be revised; and to determine a grade that described the quality of the overall evidence and a grade for the strength of each recommendation.

Grading

A structured approach—modeled after Grading of Recommendations Assessment, Development and

Evaluation (GRADE) and facilitated by the use of evidence profiles and evidence matrices—was used to determine a grade that described the quality of the overall evidence and a grade for the strength of a recommendation. For each topic, the discussion on grading of the quality of evidence was led by the ERT, and the discussion regarding the strength of the recommendations was led by the Work Group Chairs.

Grading the Quality of Evidence for Each Outcome

The "quality of a body of evidence" refers to the extent to which the Work Group's confidence in an estimate of effect is sufficient to support a particular recommendation. Following GRADE, the quality of a body of evidence pertaining to a particular outcome of interest is initially categorized on the basis of study design. For questions of interventions, the initial quality grade is "high" if the body of evidence consists of RCTs, "low" if it consists of observational studies, or "very low" if it consists of studies of other study designs. For questions of interventions, the Work Group graded only RCTs. The grade for the quality of evidence for each intervention–outcome pair was then decreased if there were serious limitations to the methodological quality of the aggregate of studies; if there were important inconsistencies in the results across studies; if there was uncertainty about the directness of evidence including a limited applicability of findings to the population of interest; if the data were imprecise or sparse; or if there was thought to be a high likelihood of bias. The final grade for the quality of evidence for an intervention–outcome pair could be 1 of the following 4 grades: "high," "moderate," "low," or "very low" (see the "Rating Scheme for the Strength of the Evidence" field).

Grading the Overall Quality of Evidence

The quality of the overall body of evidence was then determined on the basis of the quality grades for all outcomes of interest, taking into account explicit judgments about the relative importance of each outcome. The resulting final categories for the quality of overall evidence were A, B, C, and D (see the "Rating Scheme for the Strength of the Evidence" field). This grade for overall evidence is indicated behind the strength of recommendations. The summary of the overall quality of evidence across all outcomes proved to be very complex. Thus, as an interim step, the evidence profiles recorded the quality of evidence for each of 3 outcome categories: patient-centered outcomes, other bone and vascular surrogate outcomes, and laboratory outcomes. The overall quality of evidence was determined by the Work Group and is based on an overall assessment of the evidence. It reflects that, for most interventions and tests, there is no high-quality evidence for net benefit in terms of patient-centered outcomes.

Assessment of the Net Health Benefit across All Important Clinical Outcomes

Net health benefit was determined on the basis of the anticipated balance of benefits and harm across all clinically important outcomes. The assessment of net health benefit by the Work Group and ERT is summarized in one of the following statements: (i) There is net benefit from intervention when benefits outweigh harm; (ii) there is no net benefit; (iii) there are trade-offs between benefits and harm when harm does not altogether offset benefits but requires consideration in decision making; or (iv) uncertainty remains regarding net benefit (see Table 6 in the original guideline document).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Overview of the Process

The process of updating the guideline consisted of the following steps:

- Convening of a Controversies Conference to determine whether sufficient new data exist to support a reassessment of the guideline

Appointing a Work Group and an Evidence Review Team (ERT)
Refining the research questions
Developing the search strategy, inclusion/exclusion criteria, and data extraction tables
Drafting the evidence matrices and evidence profiles
Revising the recommendations
Grading the quality of the evidence
Grading the strength of the recommendation

Controversies Conference

In October 2013, Kidney Disease: Improving Global Outcomes (KDIGO) held a Controversies Conference entitled "Chronic Kidney Disease—Mineral and Bone Disorder (CKD-MBD): Back to the Future," in Madrid, Spain. The purpose of the conference was to determine whether there was sufficient new evidence to support updating any of the recommendations from the 2009 KDIGO guideline on the diagnosis, evaluation, prevention, and treatment of CKD-MBD. Seventy-four experts in adult, pediatric, and transplant nephrology, endocrinology, cardiology, bone histomorphometry pathology, and epidemiology attended the conference.

Four topic areas were considered: (i) vascular calcification; (ii) bone quality; (iii) calcium and phosphate; and (iv) vitamin D and parathyroid hormone (PTH). Each participant was assigned to 1 of the 4 topics based on their area of expertise. Participants identified new studies in their topic area and answered a set of questions to determine which recommendations required reevaluation.

The result was a list of recommendations to be addressed in a selected update (i.e., to use specific methods to update only those parts of the guideline in need of update). There was a public review of the scope of work for the guideline.

Appointment of Guideline Work Group and Evidence Review Team

The KDIGO Co-Chairs appointed 2 chairs of the Guideline Work Group, who then assembled the Work Group to be responsible for the development of the guideline. The Work Group comprised domain experts, including individuals with expertise in adult and pediatric nephrology, bone disease, cardiology, and nutrition. The Johns Hopkins University in Baltimore, MD, was contracted as the ERT to provide expertise in guideline development methodology and systematic evidence review. KDIGO support staff provided administrative assistance and facilitated communication.

The ERT consisted of methodologists with expertise in nephrology and internal medicine, and research associates and assistants. The ERT and the Work Group worked closely throughout the project. In January 2015, the ERT and the Work Group Co-Chairs held a 2-day meeting in Baltimore, MD, to discuss the guideline development and systematic review processes and to refine the key questions.

The ERT performed systematic reviews for each of the questions conducting literature searches, abstract and full-text screening, data extraction, risk of bias assessment, and synthesis. The ERT provided suggestions and edits on the wording of recommendations, and on the use of specific grades for the strength of the recommendations and the quality of evidence. The Work Group took on the primary role of writing the recommendations and rationale, and retained final responsibility for the content of the recommendations and for the accompanying narrative.

Refinement of the Research Questions

The first task was to define the overall topics and goals for the guideline. Using the recommendations identified during the Controversies Conference, the ERT drafted research questions and identified the population, interventions, comparison, and outcomes (PICO elements) for each research question.

The ERT recruited a technical expert panel to review the research questions. The technical expert panel included internal and external clinicians and researchers in nephrology and CKD. During a conference call, the technical expert panel provided feedback on the research questions.

The Work Group Co-Chairs and the ERT refined the research questions at the 2-day meeting in Baltimore,

MD. During this meeting decisions were also made about outcomes, including those considered most important for decision making that would be graded (key outcomes). The finalized research questions and outcomes are presented in Table 2 in the original guideline document.

Revising Recommendations

In June 2015, the Work Group and the ERT convened a 3-day meeting in Baltimore, MD, to review the summary tables, evidence profiles, and evidence matrices; to decide whether and how the recommendations should be revised; and to determine a grade that described the quality of the overall evidence and a grade for the strength of each recommendation.

Grading

A structured approach—modeled after Grading of Recommendations Assessment, Development and Evaluation (GRADE) and facilitated by the use of evidence profiles and evidence matrices—was used to determine a grade that described the quality of the overall evidence and a grade for the strength of a recommendation. For each topic, the discussion on grading of the quality of evidence was led by the ERT, and the discussion regarding the strength of the recommendations was led by the Work Group Chairs.

Grading the Recommendations

The "strength of a recommendation" indicates the extent to which one can be confident that adherence to the recommendation will do more good than harm. The strength of a recommendation is graded as Level 1 or Level 2. The nomenclature for grading the strength of a recommendation and the implications of each level for patients, clinicians, and policy makers are provided in the "Rating Scheme for the Strength of the Recommendations" field. Recommendations can be for or against doing something. Table 8 in the original guideline document shows that the strength of a recommendation is determined not just by the quality of evidence, but also by other, often complex judgments regarding the size of the net medical benefit, values and preferences, and costs.

Ungraded Statements

The Work Group felt that having a category that allows it to issue general advice would be useful. For this purpose, the Work Group chose the category of a recommendation that was not graded. Typically, this type of ungraded statement met the following criteria: it provides guidance on the basis of common sense; it provides reminders of the obvious; and it is not sufficiently specific enough to allow an application of evidence to the issue, and therefore it is not based on a systematic evidence review. Common examples include recommendations regarding the frequency of testing, referral to specialists, and routine medical care. The ERT and Work Group strove to minimize the use of ungraded recommendations.

Formulation and Vetting of Recommendations

Recommendations were drafted to be clear and actionable, and the wording also considered the ability of concepts to be translated accurately into other languages. The final wording of recommendations and corresponding grades for the strength of the recommendations and the quality of evidence were voted upon by the Work Group and required a majority to be accepted.

Rating Scheme for the Strength of the Recommendations

Implications of the Strength of a Recommendation

	Implications		
Grade*	**Patients**	**Clinicians**	**Policy**
Level 1 "The Work Group	Most people in your situation would want the recommended	Most patients should receive the recommended course of action.	The recommendation can be adopted as a policy in most situations.

recommends"	course of action and only a small proportion would not.	Implications	
Grade*	**Patients**	**Clinicians**	**Policy**
Level 2 "The Work Group suggests"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

*The additional category "not graded" is used, typically, to provide guidance based on common sense or when the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The process of peer review included an external review by the public to ensure widespread input from numerous stakeholders, including patients, experts, and industry and national organizations. All feedback received was reviewed and considered by the Work Group before finalizing this guideline document for publication.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- A *post hoc* analysis demonstrated efficacy of denosumab in decreasing fracture risk and increasing bone mineral density (BMD) in 2817 women with chronic kidney disease (CKD) G3a–G3b and 73 with CKD G4. The growing experience with osteoporosis medications in patients with CKD increases the comfort of treating patients with low BMD and a high risk of fracture with antiresorptive therapy, although definitive trials are lacking.
- A recent Cochrane review examined vitamin D therapy for bone disease in children with CKD G2 to G5 on dialysis. Bone disease, as assessed by changes in parathyroid hormone (PTH) levels, was

improved by all vitamin D preparations regardless of route or frequency of administration.

Refer to the "Rationale" sections following each recommendation for discussions of potential benefits and the risk-benefit ratio of individual recommendations.

Potential Harms

- In patients with chronic kidney disease (CKD) G3a–G5D with biochemical abnormalities of chronic kidney disease—mineral and bone disorder (CKD-MBD) and low bone mineral density and/or fragility fractures, treatment choices should take into account specific side effects (e.g., antiresorptives will exacerbate low bone turnover, denosumab may induce significant hypocalcemia), and the risk of their administration must be weighed against the accuracy of the diagnosis of the underlying bone phenotype.
- The Work Group voted to remove the requirement of bone biopsy prior to the use of antiresorptive therapy for osteoporosis because the use of these drugs must be individualized in patients with CKD. However, it is still prudent that these drugs be used with caution and that the underlying renal osteodystrophy be addressed first. With regard to efficacy, one may speculate that antiresorptive therapies confer less benefit in the absence of activated osteoclasts, as is the case in adynamic bone disease. Moreover, additional side effects such as acute kidney injury may also merit consideration in CKD G3a–G5.
- Even calcium-free binders may possess a potential for harm (e.g., due to side effects such as gastrointestinal distress and binding of essential nutrients).
- In recognition of the unique calcium demands of the growing skeleton, PTH-lowering therapies should be used with caution in children to avoid hypocalcemia.

Refer to the "Rationale" sections following each recommendation for discussions of potential benefits and the risk-benefit ratio of individual recommendations. Adverse events reported in studies are summarized in the evidence tables accompanying the original guideline document (see the "Availability of Companion Documents" field).

Qualifying Statements

Qualifying Statements

To the fullest extent of the law, neither KDIGO, Kidney International Supplements, nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

Use of the Clinical Practice Guideline

This Clinical Practice Guideline Update is based upon systematic literature searches last conducted in September 2015 supplemented with additional evidence through February 2017. It is designed to assist decision making. It is not intended to define a standard of care, and should not be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Health care professionals using these recommendations should decide how to apply them to their own clinical practice.

Limitations of Approach

Although the literature searches were intended to be comprehensive, they were not exhaustive. MEDLINE and Cochrane CENTRAL were the only databases searched, and the search was limited to English language publications. Hand searches of journals were not performed, and review articles and textbook

chapters were not systematically searched. However, Work Group members did identify additional or new studies for consideration.

Nonrandomized studies were not systematically reviewed for studies of interventions. The Evidence Review Team (ERT) and Work Group resources were devoted to review of randomized trials, as these were deemed most likely to provide data to support treatment recommendations with higher-quality evidence.

Evidence for patient-relevant clinical outcomes was low. Usually, low-quality evidence required a substantial use of expert judgment in deriving a recommendation from the evidence reviewed.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney diseaseâ€"mineral and bone disorder (CKD-MBD). Kidney Int Suppl. 2017 Jul;7(1):1-59. [173 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2017 Jul

Guideline Developer(s)

Kidney Disease: Improving Global Outcomes - Nonprofit Organization

Source(s) of Funding

Kidney Disease: Improving Global Outcomes (KDIGO)

Guideline Committee

Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group

Composition of Group That Authored the Guideline

Work Group Co-chairs: Markus Ketteler, MD, FERA; Klinikum Coburg, Coburg, Germany; Mary B. Leonard, MD, MSCE, Stanford University School of Medicine, Stanford, CA, USA

Work Group Members: Geoffrey A. Block, MD, Denver Nephrology, Denver, CO, USA; Pieter Evenepoel, MD, PhD, FERA, University Hospitals Leuven, Leuven, Belgium; Masafumi Fukagawa, MD, PhD, FASN, Tokai University School of Medicine, Isehara, Japan; Charles A. Herzog, MD, FACC, FAHA, Hennepin County Medical Center, Minneapolis, MN, USA; Linda McCann, RD, CSR, Eagle, ID, USA; Sharon M. Moe, MD, Indiana University School of Medicine, Roudebush Veterans Affairs Medical Center, Indianapolis, IN, USA; Rukshana Shroff, MD, FRCPCH, PhD, Great Ormond Street Hospital for Children, NHS Foundation Trust, London, UK; Marcello A. Tonelli, MD, SM, FRCPC, University of Calgary, Calgary, Canada; Nigel D. Toussaint MBBS, FRACP, PhD, The Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia; Marc G. Vervloet, MD, PhD, FERA, VU University Medical Center Amsterdam, Amsterdam, The Netherlands

Evidence Review Team (Johns Hopkins University Baltimore, MD, USA): Karen A. Robinson, PhD, Associate Professor of Medicine and Project Director; Casey M. Rebholz, PhD, MPH, MS, Co-investigator; Lisa M. Wilson, ScM, Project Manager; Ermias Jirru, MD, MPH, Research Assistant; Marisa Chi Liu, MD, MPH, Research Assistant; Jessica Gayleard, BS, Research Assistant; Allen Zhang, BS, Research Assistant

Financial Disclosures/Conflicts of Interest

Kidney Disease: Improving Global Outcomes (KDIGO) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise as a result from an outside relationship or a personal, professional, or business interest of a member of the Work Group. All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived as or are actual conflicts of interest. This document is updated annually and information is adjusted accordingly. All reported information is published in its entirety at the end of the original guideline document in the Work Group members' Biographical and Disclosure Information section, and is kept on file at KDIGO.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int. 2009 Aug;76(Suppl 113):S1-130. [477 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Kidney Disease: Improving Global Outcomes (KDIGO) Web site .

Availability of Companion Documents

The following are available:

Ketteler M, Block GA, Evenepoel P, Fukagawa M, Herzog CA, McCann L, Moe SM, Shroff R, Tonelli MA, Toussaint ND, Vervloet MG, Leonard MB. Executive summary of the 2017 KDIGO chronic kidney disease-mineral and bone disorder (CKD-MBD) guideline update: what's changed and why it matters. Kidney Int. 2017 Jul;92(1):26-36. Available from the Kidney Disease: Improving Global Outcomes (KDIGO) Web site .

Summary of 2017 KDIGO CKD-MBD guideline recommendations. New York: Kidney Disease: Improving Global Outcomes; 2017 Jul. 2 p. Available from the KDIGO Web site .

KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease—mineral and bone disorder (CKD-MBD). Appendices A and B. New York: Kidney Disease: Improving Global Outcomes; 2017 Jul. 2 p. Available from the KDIGO Web site .

KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease—mineral and bone disorder (CKD-MBD). Evidence summary tables. New York: Kidney Disease: Improving Global Outcomes; 2017 Jul. 179 p. Available from the KDIGO Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on October 26, 2012. This summary was updated by ECRI Institute on July 3, 2017. The updated information was verified by the guideline developer on August 15, 2017.

This NEATS assessment was completed by ECRI Institute on July 25, 2017. The information was verified by the guideline developer on August 15, 2017.

Copyright Statement

Disclaimer

NGC Disclaimer

The National Guideline Clearinghouseâ„¢ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria.

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.